

A STUDY OF EPITHELIAL OVARIAN MALIGNANCY & ITS TREATMENT IN A TERTIARY HOSPITAL

*A Dissertation submitted to
The Tamil Nadu Dr.M.G.R. Medical University
in partial fulfillment of the regulation for the award
of the degree of MD, (Branch II)
Obstetrics and Gynecology*



**MADRAS MEDICAL COLLEGE
CHENNAI – 600 003.**

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This is to certify that Dissertation is

submitted by

Dr. S. Manjula

To the Tamil Nadu Dr. M.G.R. University

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Obstetrics and Gynecology

INTRODUCTION

Of all gynecologic cancers, ovarian malignancies represent the greatest clinical challenge. Epithelial ovarian malignancies are the most common type of ovarian malignancy. Epithelial Ovarian Cancers (EOC) can occur in females as young as 15 years, but the mean age is 56 years. Epithelial Ovarian cancers (EOC) are the most commonly in white women in the industrialized countries of northern and western Europe and North America and least commonly in India and Asia.

Patients have advanced disease at diagnosis in more than two-thirds of the cases. It has the highest fatality-to-case ratio of all the gynaecologic malignancies.

EOC is responsible for 2% all cancers and 2.9 % cancer deaths.

Incidence: 0.7/1 lakh women at 20 years 5/1lakh women at 40 years 30-40/1lakh women at > 60 years.

The incidence of EOC is highest in the Scandinavian countries. 22.2%.

From ICMR & IARC. Lit.

Switzerland	16.3
UK	12.4
Delhi	10.2
Mumbai	8.8
Trivandram	6.3
Bhopal	5.7
Chennai	5.3
Bangalore	5.1
Japan	2.7
US (Native Whites)	0.5
US (Native Blacks)	0.1

Rate 1/1, 00, 000

Pathology

EOC tumors are found as partially cystic lesions with solid components.

The surface may be smooth or covered in papillary projections and the cysts contain fluid ranging from straw-colored to opaque brown or hemorrhagic. EOC is thought to arise from epithelium covering the ovaries, which is derived from the coelomic

epithelium in fetal development. This coelomic epithelium also is involved in formation of the mullerian ducts, from which the fallopian tubes, uterus, cervix, and upper vagina develop.

Five main histologic subtypes, which are similar to carcinoma, arise in the epithelial lining of the cervix, uterus, and fallopian tube: (1) serous (from fallopian tube), (2) endometrioid (endometrium), (3) mucinous (cervix), (4) clear cell (mesonephros), and (5) Brenner.

Predisposing Factors:

EOC is rare before the age of 40, increases steadily thereafter and peaks at the age of 65 – 75. Risk of EOC is increased in nulliparous and those with early menarche and late menopause which is explained by the theory of ‘INCESSANT OVULATION’ and by ‘GONODOTROPHIN THEORY’. A steady decreased risk is observed with increased parity and with the use of OCP.

3 Familial Ovarian cancer syndromes have been described.

- HBOC (Hereditary breast , Ovary cancer Syndrome)
- Hereditary site specific ovarian cancer syndrome
- Lynch syndrome – Type II
- which were inherited by autosomal dominant transmission.

In family with 2 first Degree relatives (mother, sister, daughter) with premenopausal EOC likelihood of a female relative having an affected BRAC 1 or BRAC 2 gene is as 40%.

Individuals with a mutation of BRCA 1 Gene have a 50-85% lifetime risk of developing breast cancer & 15 to 45% risk of developing EOC.

Individuals within a mutation of BRCA 2 have a 50-85% percent developing breast Cancer & 10 to 20% risk of developing EOC.

Mutations have been demonstrated in mismatch repair genes MSH1, MSH2, PMS1, PMS2.

Assessment of risk of malignancy in EOC

- i. Fixed or irregular consistency on Pelvic Examination.
- ii. Solid or papillary projections on Transvaginal Sonography.
- iii. A serum CA 125 $> 35 \mu$ per ML.
- iv. A pulsatility Index < 1 or Resistive Index < 0.4 on color Doppler.

If all 4 indicators are positive in a post menopausal woman, the risk for malignancy is 83%. In contrast if all indicators are negative, 100% had benign ovarian tumor.

Other Risk Factors Polycystic ovary disease, diet high in saturated animal fats, family history – 10% cases have genetic predisposition.

Presentation patients with ovarian cancer typically show few signs or symptoms until the disease is widely spread throughout the abdomen.

Non- specific GI symptoms are common, e.g. nausea, dyspepsia common, e.g. nausea, dyspepsia and altered bowel habit. May be a sensation of pelvic weight or pressure. Early satiety and abdominal distension occur in advanced disease.

In women of reproductive age, menstrual abnormalities are seen in approx. 15% of Patients.

Diagnosis

Presence of advanced ovarian cancer often is suspected on clinical grounds but can be confirmed only pathologically by removal of the ovaries or, when disease is advanced, by sampling tissue or ascitic fluid.

Ultrasound Imaging is the most useful initial investigation in a patient found to have a pelvic mass. This may define the morphology of the pelvic tumor. In addition, it can determine whether large masses are present in other parts of the abdomen, including in the liver. This technique also can be used to evaluate the kidneys for evidence of ureteric obstruction and to detect ascites.

CT scan with oral and intravenous contrast can detect intra abdominal disease and help evaluate for pelvic sidewall disease. Some have suggested a role in assessing operability of the tumor. Tumor markers such as CA125 are not good discriminators of benign from malignant lesions in premenopausal women. CA125 has much better accuracy in prognostic outcome.

Patterns of spread

EOC most often spreads initially within the peritoneal cavity. Metastatic disease often is found on the peritoneal surfaces, particularly on the undersurface of the diaphragm, the paracolic gutters, the bladder, and the cul-de-sac. Other common sites are the surface of the liver, the mesentery and serosa of the large and small bowel, in the omentum, the uterus, and paraaortic and pelvic lymph nodes. Outside the peritoneal cavity, EOC may spread to the pleural cavity, lungs, and groin lymph nodes. Presence of pleural effusion does not necessarily indicate disease in the chest, and malignancy can be diagnosed only cytologically. Mucinous tumors tend to form large dominant masses, while papillary serous tumors have a more diffuse distribution and are more commonly bilateral. Endometrioid and clear-cell variants more commonly exhibit local invasion and retroperitoneal disease.

Staging

EOC is staged according to *Federation International de Gynecologie et Obstetrique* (FIGO) (ie, International Federation of Gynecology and Obstetrics) rules as follows:

Stage I - Growth limited to the ovaries.

- IA - Growth limited to 1 ovary, no ascites present containing malignant cells, no tumor on the external surface, capsule intact.
- IB - Growth limited to both ovaries, no ascites present containing malignant cells, no tumor on the external surfaces, capsules intact.
- IC* - Tumor either stage IA or IB, but with tumor on surface of 1 or both ovaries with capsule ruptured, with ascites present containing malignant cells, or with positive peritoneal washings.

• **Stage II** - Growth involving 1 or both ovaries with pelvic extension.

- IIA - Extension and/or metastases to the uterus and/or tubes.

- IIB - Extension to other pelvic tissues.
- IIC* - Tumor either stage IIA or IIB, but with tumor on surface of 1 or both ovaries, with capsule(s) ruptured, with ascites present containing malignant ovaries, or with positive peritoneal washings.
- **Stage III** - Tumor involving 1 or both ovaries with histologically confirmed peritoneal implants outside pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis equals stage III; tumor limited to true pelvis, but with histologically proven malignant extension to small bowel and omentum.
 - IIIA - Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel mesentery.
 - IIIB - Tumor of 1 or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative.

- **IIIC** - Peritoneal metastasis beyond the pelvis larger than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
- **Stage IV** - Growth involving 1 or both ovaries with distant metastases; if pleural effusion is present, positive cytology must be apparent to allot a case to stage IV; parenchymal liver metastasis qualifies as stage IV disease.

Surgery for ovarian cancer.

Ovarian epithelial malignancies are staged according to the FIGO system. The importance of thorough surgical staging cannot be overemphasized, because subsequent treatment will be determined by the stage of disease.

Technique for surgical staging:

For patients where pre op evaluation suggests a probable malignancy , a midline or paramedian abdominal incision is recommended to allow adequate access tom the upper abdomen.

- Aspirate ascitic fluid for cytology studies.
- Perform peritoneal washings for cytology if ascites is not present.
- Remove the ovary and ovarian tumor intact.
- Perform diaphragmatic scraping for cytology studies.
- Obtain peritoneal biopsy specimens.
- Perform a subcolic omentectomy.
- Obtain bilateral paraaortic and pelvic node samples.
- Obtain biopsy samples of adhesions or other suspicious areas.
- If the patient does not desire future fertility, perform a total abdominal hysterectomy and excise the opposite ovary.
- Remove the appendix if mucinous tumor is present.
- All visible tumor should be removed. This may require extensive surgery, including bowel resection, excision of peritoneal implants, liver resection, omentectomy, and splenectomy.

- The extent of bowel resection should depend on the role this plays in achieving maximal cytoreduction.

*Fluid must have been in contact with broad surfaces of the peritoneum above the liver, the paracolic gutters, and the pelvis. All specimens may be placed in the same container with heparin and 1 U/mL of aspirate and sent for cytology studies.

Early Stages EOC Risk Groups.

Low Risk

Stage IA or IB, Grade 1 & 2

High Risk

Stage IA or IB, Grade 3

Stage IC All Stage II

PROGNOSIS

Epithelial stage I	76 – 93%
Epithelial stage II	60 – 74%
Epithelial stage III	23 – 41%
Epithelial stage IV	11%

REVIEW OF LITERATURE

In 1809 McDowell successfully removed a diseased ovary and the patient survived. This Kentucky frontier physician did 13 “ovariotomy” operations. Eight women survived the surgery. McDowell’s initial experience was the first time that a diseased intra-abdominal organ was successfully removed and the patient lived. Nevertheless, it took almost another half century before the routine removal of diseased ovaries became an accepted surgical practice. The diseased ovaries removed were invariably thought preoperatively, to be benign. Tate introduced the concept of an exploratory laparotomy in 1879 as he believed that benign ovarian tumors might be mistaken for ovarian cancer. It was the dogma of that era that one never operated on ovarian cancer because the surgery did little good and it had no impact on the ultimate survival of the patient. By the beginning of the 1900’s surgeons were routinely operating on women thought to have ovarian cancer in an effort to remove the diseased organ.

In 1935, Lynch reported a landmark paper in the management of ovarian cancer. He observed that ovarian cancer appeared to be familial, that most of the patients alive at 5 years either had borderline malignant potential tumors or had well differentiated cancers of the ovary and that

one third of the women alive at 5 years were alive with disease. The latter invariably died 7-8 years following the original diagnosis. In 1940, Pemberton introduced the idea of an omentectomy as part of the initial management of ovarian cancer. In 1968, Munnell reported his aggressive surgical approach to the management of ovarian cancer which included resection of the sigmoid colon when the disease apparently was confined to the pelvis. However, it was Griffiths¹⁰ retrospective study that demonstrated that when women were operated on with advanced stage ovarian cancer and residual disease >1.5 cm in maximum diameter were left in the abdominal cavity, these patients almost invariably were dead in 2 years. When patients were operated on and were found to have intra-abdominal carcinomatosis but only miliary seedings, i.e. tumor implants <1.5 cm in maximum diameter, in the upper abdomen, such patients had a 5 year survival of approximately 20%. Griffiths then demonstrated, in a third group of patients, when large volume disease was present in the upper abdomen and he was able to surgically cytoreduce the cancer

such that at the end of the operation the residual disease was <1.5 cm in maximum diameter, these patients had a prolonged survival with 20% alive at 5 years. It was this retrospective review by Griffiths that

established the concept of aggressive surgery followed by aggressive chemotherapy as the ideal way to manage advanced stage ovarian cancer.¹²

In non-randomized studies, Piver, et al & Dottins, et al have reported excellent survival rates > 90% in patients treated with cisplatin based chemotherapy.

Rubin et al. reviewed 62 patients with stage I EOC. All of them underwent comprehensive surgical staging followed platinum based chemotherapy. 15 patients relapsed (22.4%). No patient was rendered disease free after relapse. Patients with grade 3 tumors & clear cell histology had a higher risk of relapse.

GOG Study

Cisplatin versus paclitaxel versus Cisplatin and paclitaxel in patients with suboptimal stage III & IV .The combination

therapy had a better toxicity profile. Therefore combination of cisplatin and paclitaxel remains preferred initial treatment option.

Randomized intergroup trial of cisplatin and paclitaxel versus cisplatin cyclophosphamide in women with advanced EOC - **GOG 3 years results :**

Incorporating paclitaxel into 1st Line therapy improves duration and also improve Progression free survival and of Over all survival in women with incompletely resected stage III & IV EOC.

GI COG study : Comparing cisplatin with Intraperitoneal Chronic Phosphate in patient with IA, IB grade 1 & 2 & IC disease.

Cisplatin groups had a better DFS, but OS was not significantly different compared with other arm.

GOG trial of cisplatin cyclophosphamide for 3 cycles versus Intraperitoneal Chronic Phosphate in highrisk early stage DOC.

Relapse free rate – 77% for chemotherapy arm.

66% for 32 p.arm.

GOG Randomized study between 3 versus 6 cycles of paclitaxel & carboplatin.

This trial is obviously testing the potential benefit of so called “maintenance therapy”.

AIM OF STUDY

- i. To assess treatment results in Ca ovary.
- ii. Progression free time in patients with sub-optimal cyto-reduction following adjuvant chemotherapy.
- iii. To assess the need for Neo – Adjuvant Chemotherapy in advanced Ca ovary.

SUBJECTS & METHODS

A prospective analysis of 112 patients with ovarian cancer who had been admitted in Institute Of Obstetrics & Gynaecology (IOG) Government Hospital for Women and Children between Jan-2004 and August 2005(18 months study).

Patients who had been admitted with Ovarian Cancer at Institute of Obstetrics & Gynecology (IOG) Government Hospital for Women and Children and then registered at Medical Oncology Dept., IOG were analysed.

A thorough evaluation of history & clinical findings were done for all patients.

All patients had Complete haemogram, Liver Function Test, Renal Function Test, CXR, ECG.

UltraSonoGram: Pelvis and Abdomen & Computed Tomogram Abdomen were used to assess the extent of the tumor, in the Pelvis & Abdomen especially for the presence of Peritoneal, omental deposits, sub- diaphragmatic deposits, Para-aortic nodes, liver and spleen metastasis.

Serum Tumor markers like CA 125 estimation was done wherever feasible.

According to laprotomy findings,

Patients are classified into 3 Groups.

- i. **Optimal Cyto Reduction** : Residual disease <2cm in maximal diameter. (**GRIFFITHS Criteria**)
- ii. **Sub Optimal Reduction** : Residual disease >2cm in maximal diameter. (**GRIFFITHS Criteria**)
- iii. **Open & Close** : Only BX from tumor and omentum were taken.

88 patients had EOC.

11 of 88 patients were in Early stage.

77 of 88 patients were in Advanced stage.

64 had Adjuvant chemotherapy after laparotomy.

13 had Neo- Adjuvant chemotherapy.

Adjuvant Chemotherapy with Cisplatin 75 mg. /m² & Cyclophosphamide 750 mg. /m² given for a period of 3 days every three weekly for a period of 6 cycles. Chemotherapy was started within 14 days of laprotomy.

Occasional patients were given Chemotherapy with Carboplatin & Cyclophosphamide or single agent Carboplatin.

13 of 77 Patients are treated with Neo Adjuvant chemotherapy who presented with advanced stage ovarian cancer and were medically disabled, with the same dose of Chemotherapy. One patient had Carboplatin & Cyclophosphamide

Toxicity :

Observed we are Gastro Intestinal symptoms in the form of nausea and vomiting, Haematological – anemia, neutropenic fever, Neurological - peripheral neuropathy which were noted after 6 months of chemotherapy.

Follow Up :

Patients are followed-up once in 3 months with Pelvic Examination, USG, tumor marker (whenever feasible) for 2 years, once in six months for the next three years & once in a year for life long.

RESULTS

Patients with EOC admitted from Jan 2004 to Aug 2005 were observed.

Table – 1
Types of Ovarian Cancer cases

Epithelial	88	77%
Border line Epithelial cell cancer	05	4.4%
Germcell Tumour	09	10%
Sexcord Stromal cell Tumour	07	6%
Others –Krukenberg	02	2.6%
Non- Hodgkin lymphoma	01	
TOTAL	112	

78.5% of Ovarian cancer cases admitted were Epithelial Ovarian Cancer.

Table – 2
Age distribution for Ovarian Cancer

Age in years	No.of cases	Percentage
10 - 19	6	5
20 - 29	17	15
30 - 39	18	15.8
40 - 49	43	38.9
50 - 59	19	16.8
60 - 69	3	2.6
70 - 79	6	5.3

Median Age : 45 yrs

Table – 3**Age Distribution for EOC**

Age in years	No. of cases	Percentage
20-29	10	8.8
30-39	14	16
40-49	39	44.2
50-59	16	18.2
60-69	3	3.4
70-79	6	6.8

Median age 45 Years

Table - 4**PARITY**

Parity	No.of Cases	Percentage
NULLIPAROUS	25	28%
1-2 CHILDREN	23	26%
>2 CHILDREN	52	56%

28% of 112 patients were Nulliparous.

Table – 5
Histological Types of EOC.

Total No of EOC	88	
Serous	66	75%
Mucinous	17	20%
Endometrioid	02	02%
Others	03	03%

66 of 88 patients treated conventionally with surgical debulking had
Serous carcinoma.

Table – 6

Epithelial cell tumours	88	
Early Stage	11	(12.5%)
Advanced Stage III & IV	77	(87.5%)

77 (87.5%) of 88 patients are in Advanced Stage.

Table - 7**LAPAROTOMY RESULTS**

Sub Optimal Cyto reduction	52	(81.25%)
Open & Close	12	(18.75%)
Total	64	

(Residual disease > 2cm in in maximal diameter)

All patients had Total Abdominal Hysterectomy and Bilateral Salpingo
Oophorectomy, partial omentectomy.

Table – 8

Treatment given :

Adjuvant chemotherapy	64
Neo- Adjuvant chemotherapy	13

Table 9**Adjuvant Chemotherapy Schedule in Advanced EOC.**

<i>Drugs</i>	<i>Dose</i>	<i>Interval</i>	<i>Period of Treatment</i>	<i>No :</i>
Cisplatin & Cyclophosphamide	75mg/m ² 750 mg/m ²	Every 3 weeks	6 cycles	63
Carboplatin & Cyclophosphamide	AUC 5- 6 75mg/m ²	Every 4 weeks	6 cycles	1

63 patients had combination chemotherapy with Cisplatin 75 mg/m² and Cyclophosphamide 750 mg/m² every 3 weeks for a total period of 6 cycles.

1 patient had single dose Carboplatin in Adjuvant Chemotherapy.

Table -10**Neo - Adjuvant Chemotherapy Schedule in Advanced EOC.**

<i>Drugs</i>	<i>Dose</i>	<i>Interval</i>	<i>Period of Treatment</i>	<i>No :</i>
Cisplatin & Cyclophosphamide	75mg/m ² 750 mg/m ²	Every 3 weeks	3 cycles	12
Carboplatin	AUC 5-6	Every 4 weeks	3 cycles	1

12 patients had combination Chemotherapy Cis platin 75 mg/m² with Cyclophosmamide 750 mg/m² every 3 weeks for a total period of 3 cycles. 1 patient had single dose Carbo platin in Neo Adjuvant Chemotherapy.

Table- 11

	Adjuvant Chemotherapy	Neo-Adjuvant Chemotherapy
Lost Follow-up	18	6
Death	2	1

Table – 12**Toxicity**

Gastro - Intestinal	80%
Haematological	20%
Neurotoxicity	20%

Table – 13

**Median Time to Progression in Patients after Adjuvant
Chemotherapy**

Suboptimal –reduction	9 months
Open & Close	6 months

Table – 14

Median Time to Progression in Patients after Neo- Adjuvant Chemotherapy
9 months

Table - 15**Progression free Survival following**

	>12months	< 12 months
Adjuvant Chemotherapy After Suboptimal - reduction	11	13
Neo Adjuvant Chemotherapy	4	0

RESULTS

The high mortality from ovarian cancer reflects a lack of an effective screening procedure. The 5 year survival for the majority of patients with this disease (FIGO stage III & IV) is approximately 20%. Although dramatic improvements in treatment have led to prolonged disease free survival for the overwhelming majority of these women with stage III & IV disease, intense cytoreductive surgery followed by chemotherapy is only palliative treatment.

78.5% ovarian cancer belong to the malignant EOC (Refer Table—1) which correlates well with the statistics of Jemal A.etal & Young a study on cancer statistics which states that 90 % of ovarian tumors belong to EOC. The median age of ovarian cancer is 45 years (Refer Table-2) which is 1-2 decade less than the age observed by Truong LD et al (55-65 years). The median age of EOC is 45 years(Refer Table3) which is one decade less than study observed by Procorelli S. Odicini F, the peak incidence of EOC is at 56 to 60 years of age.

EOC has been associated with increase in parity > 2 children i.e.,(57%) (Refer Table 4) which is in contrast with the study of Negrietal in which nulliparous women has the highest incidence-(a study of reproductive factor and risk of EOC) which states that ovarian cancer

has been associated with low parity and infertility. Early menarche and late menopause increase the risk of ovarian cancer. (Franceschi S¹ et al). The suppression of ovulation may be an important factor.

66 of 88 patients treated conventionally with surgical debulking had Serous Ca, (Refer Table 5) which correlates well with the study of Scully R, Young R H in which 75 % of EOC are of Serous histologic type. Less common are mucinous (20 %) endometrioid (2%), others (3%).

According to Laparotomy results 11 patients of 88 were Early stage. 64 of 88 patients were in Advanced stage (Refer Table 6). 64 patients of 88 had Sub optimal cyto reduction in our Institute. including 12 cases of Open & Close cyto reduction. (Refer Table 7)

11 patients in Early stage had no recurrence till the last day of follow up, to whom no chemotherapy was given. The primary surgical treatment they had undergone was total abdominal hysterectomy and bilateral salpingo oophorectomy. In certain circumstances, an unilateral oophorectomy was performed.

Adjuvant Chemotherapy

63 of 77 patients had combination chemotherapy with cisplatin and cyclophosphamide (Refer Table 8)

44 patients had completed combination Chemotherapy of Cis platin 75 mg/m^2 with Cyclophosphamide 750 mg/m^2 every 3 weeks for a total period of 6 cycles. 1 patient had single dose Carbo platin in Adjuvant Chemotherapy.(Refer Table 9).

DISEASE FREE SURVIVAL

13 patients had DFS until 12 months.

11 patients had DES > 12 months

18 patients lost follow up

2 deaths occurred

PROGRESSION FREE SURVIVAL

11 patients are living more than 12 months without any recurrence

13 patients are living 6 – 12 months without any recurrence. (Refer Table 15)

Neo Adjuvant Chemotherapy

12 of 13 patients had combination Chemotherapy every 3 weeks Cisplatin 75 mg/m² with Cyclophosphamide 750 mg/m² every 3 weeks over 3 cycles. 1 patient had single dose Carboplatin in Neo Adjuvant Chemotherapy. (Refer Table 10)

5 patients lost follow-up and one patient died during Neo Adjuvant Chemotherapy (Refer Table 11)

In Neo Adjuvant Chemotherapy 3 out of 13 patients had recurrences with progressive disease. 4 out of 13 patients had progression free survival. (Refer Table : 15)

Progression Free survival period for Neo Adjuvant treatment is 14 months when compared with conventionally treated women is 9 months. (Refer Table : 15)

Median Time to progression for disease for 13 women who received Neo Adjuvant Chemotherapy is 9 months versus 9 months for

64 patients who had suboptimal cytoreduction followed with Adjuvant Chemotherapy

(Ref Table : 13 & 14)

The toxicity symptoms noted were in the form of Gastro Intestinal- nausea vomiting Dyspepsia, Haematological – Anemia, Neutropenia, Neurological – peripheral neuropathy which were noted after 6 months of Chemotherapy (Ref Table : 12)

Patients after Chemotherapy were evaluated with USG/CT/TumorMarker (wherever feasible)to help to assess whether the patient had regression of disease or persistent disease.

It is our intention to proceed with a prospective randomized study comparing Neo adjuvant cisplatin and Cyclophosphamide

chemotherapy to conventional cyto reductive surgery followed by the same chemotherapy. Inclusive criteria of eligibility of this study being that the women must have cytologic evidence of a malignancy with an epithelial cancer who had conventional cyto reductive surgery followed by Adjuvant chemotherapy. Since our institution is funded by Government cost/benefit analysis of surgery and chemotherapy is not performed.

DISCUSSION

Treatment of ovarian cancer was undertaken after consideration of many factors, including the extent of disease spread, symptoms, and patients' wishes and fitness to undergo treatment.

Surgery

Surgery was the initial treatment of choice, provided patients are medically fit. Patients who were not fit for surgery were given chemotherapy and considered for surgery later. The aim of surgery was to confirm the diagnosis, define the extent of disease and resect all visible tumor. The role of cytoreduction was demonstrated by Griffiths in 1975 and has been confirmed by others.

11 patients in Early stage had no recurrence till the last day of follow up to whom no chemotherapy was given. The primary surgical treatment they had undergone was total abdominal hysterectomy and bilateral salpingo oophorectomy. In certain circumstances, an unilateral oophorectomy was performed

The role of cyto reductive surgery is based on retrospective reviews. The best candidates for cytoreductive surgery are those with limited slow growing tumors. Cyto reduction often improves function & quality of life when performed as a palliative treatment to remove a bulky symptomatic tumor. The volume reduction also diminishes the metabolic demands made on the host by the tumor.

Cytoreductive surgery is not without potential hazards. Although surgical and anesthetic techniques have improved, the inherent risks of any surgical procedure must be considered in the overall assessment of the patient. Despite careful attention to detail, there is always a potential risk of physical dissemination of disease. Furthermore, surgery-induced stress causes a transient immune suppression that could, in theory, temporarily enhance tumor growth or spread. The time spent first in planning surgery and then in recovering from surgery could delay other potentially beneficial treatments.

There was found to be partial Omentectomy and there was no Pelvic/Para-aortic clearance in some cases (Sub optimal reduction in advanced stages of EOC in our study. In addition, quality of life is likely to be significantly enhanced by removal of bulky tumor masses from the pelvis and abdomen(13).

An Analysis of the retrospective data available suggests that these operations are feasible for 70% to 90 % of patients when performed by Gynecologic Oncologists. The conventional management of EOC is aggressive cyto reductive surgery followed by Platinum-Taxane combination chemotherapy. In our Institution we have used Cisplatin & Cyclophosphamide. The role of cyto reductive surgery is based on retrospective reviews. The best candidates for cytoreductive surgery are those with limited slow growing tumors. Cyto reduction often improves function & quality of life when performed as a palliative treatment to remove a bulky symptomatic tumor. The volume reduction also diminishes the metabolic demands made on the host by the tumor.

The conventional management of EOC is aggressive cytoreductive surgery followed by Platinum-Taxane combination chemotherapy. In our Institution we have treated with Cisplatin & Cyclophosphamide.

Patients are treated with Neo-Adjuvant chemotherapy who presented with advanced stage ovarian cancer and were medically disabled.³⁻⁵ Over the ensuing decade a reasonable experience was obtained suggesting that patients who were medically unable to tolerate aggressive cytoreductive surgery at the time of their initial presentation, but who received chemotherapy and then were able to undergo cytoreductive surgery, had a survival that was quite similar to those patients who initially had large volume disease present in the upper abdomen or Stage IV disease. A decade later, neoadjuvant chemotherapy followed by aggressive surgery was introduced for patients who were not medically compromised but who, by CT scan criteria, appeared to have disease that was not surgically cytoreducible. Basically, patients with disease >2 cm in diameter in the upper abdomen that involved coating the diaphragm and was confluent with implants in the liver serosa, omentum replaced by tumor with the tumor in the omentum reaching the hilum of the spleen, porta hepatis metastases, enlarged (>2 cm) suprarenal para-aortic lymph nodes and disease in the thorax were indications to recommend neoadjuvant

chemotherapy as these preoperative CT findings were usually associated with extensive upper abdominal metastases that could not be optimally cytoreduced. Our criteria for selecting patients for neoadjuvant chemotherapy also required cytology or histology specimens consistent with ovarian cancer to be present before chemotherapy is initiated.

Neoadjuvant chemotherapy for the treatment of advanced stage ovarian cancer as employed in this presentation means that the chemotherapy is administered before any surgery is performed. Cytologic material or biopsies can be obtained using diagnostic imaging to direct the biopsy. Patients who receive neoadjuvant chemotherapy are ultimately recommended to undergo standard cytoreductive surgery. Neoadjuvant chemotherapy must be distinguished from interval debulking surgery. The latter is performed when suboptimal cytoreduction is done as the initial operation. In general patients receive 3 cycles of chemotherapy following suboptimal surgical cytoreduction then undergo interval debulking surgery. Data has been presented suggesting that those patients who have been suboptimally cytoreduced, have 3 cycles of platinum-based chemotherapy and then are optimally cytoreduced, do better than those patients who do not undergo interval cytoreductive surgery.¹⁴ However, data suggests that interval cytoreduction does not improve the results of initial suboptimal cytoreduction. Patients who are

being operated for ovarian cancer should be operated by physicians trained to do aggressive cytoreductive surgery. Conventional treatment is aggressive cytoreductive surgery followed by aggressive chemotherapy. Neoadjuvant chemotherapy for the management of ovarian cancer reverses the treatment techniques used in conventional treatment.

The major concern about neoadjuvant chemotherapy in the management in advanced stage ovarian cancer has been an issue of survival. There are now multiple studies which suggest that the survival of patients treated with neoadjuvant chemotherapy is similar to that of patients who undergo conventional treatment. There appears to be no compromise in overall survival. However, to achieve survival comparable to that of women who undergo conventional treatment, it is necessary that optimal cytoreductive surgery is performed following completion of the neoadjuvant chemotherapy. If one delays the time from completing the chemotherapy to the time of performing the surgery that resistant disease develops that is not responsive to conventional chemotherapy.

Reports from Yale-New Haven Hospital and many other sites would strongly suggest that neoadjuvant chemotherapy plays a strong role in women with advanced stage ovarian cancer that is not surgically cytoreducible. Other institutions are now using laparoscopy to assess

surgical cytoreducibility. One report suggests that all patients with Stage III disease, not just those that are non-cytoreducible, may be treated with neoadjuvant chemotherapy followed by surgery without compromising their survival. Currently reports on neoadjuvant chemotherapy for the treatment of advanced stage ovarian cancer are either retrospective or limited in patient numbers. The European Organization for the Research and Treatment of Cancer (EORTC) study is now randomizing 742 women between neoadjuvant chemotherapy (platinum and taxane) for 3 cycles followed by aggressive cytoreductive surgery followed by 3 more cycles of chemotherapy vs. conventional treatment, i.e. aggressive cytoreduction followed by 6 cycle of the combination of platinum and paclitaxel. The results of that trial will be extremely helpful in sorting out a role for neoadjuvant chemotherapy in the management of advanced stage ovarian cancer.

SUMMARY

112 patients who had been admitted with Ovarian Cancer at Institute of Obstetrics & Gynecology (IOG) Government Hospital for Women and Children and then registered at Medical Oncology Dept., IOG were analysed.

88 of 112 patients had Epithelial Ovarian Cancer.

11 of 88 patients were in Early stage had no recurrence till the last day of follow up, to whom no chemotherapy was given and were follow up.

77 of 88 patients were in Advanced stage .

64 of 77 had Adjuvant chemotherapy with Cisplatin 75 mg. /m² & Cyclophosphamide 750 mg. /m² given over 3 days every three weekly for a period of 6 cycles. Chemotherapy was started within 14 days of laprotomy.

13 of 77 patients are treated with Neo Adjuvant chemotherapy with the same dose of chemotherapy for a period of 3 cycles, were followed up.

Median time to progression for disease for 13 women who received Neo Adjuvant Chemotherapy is 9 months versus 9 months for 64 patients who had suboptimal cytoreduction followed with Adjuvant Chemotherapy

Progression Free survival period for Neo Adjuvant treatment is 14 months when compared with conventionally treated women is 9 months.

Neo adjuvant chemotherapy can be considered to improve the quality of life, surgical results and subsequently the disease progression period.

CONCLUSION

- Advanced EOC Contributes 87.5% of Ovarian Cancer.
- Median time to progression is 9 months following Sub optimal surgery and Adjuvant Chemotherapy.

- Progression Free survival period for Neo-Adjuvant treatment is 14 months. when compared with conventionally treated women is 9 months.
- Neo adjuvant chemotherapy can be considered to improve the quality of life, surgical results and subsequently the disease progression period.

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MASTER CHART

ADJUVANT CHEMO THERAPY IN OVARIAN EPITHELIAL TUMOR

S.No	AGE	Parity	ClinicalFeatures	HPE/FNAC	Stage	USG	CXR	Neo Adj	Surgery
1	4	1	1,2	1a	III	2	1		1,2
2	5	3	1,2,3	1a bt	Ia	2	1		1
3	8	3	1,3	5	IV	1,3	1	1	-
4	6	2	1,2	4	IIIc	1,3	1	1	-
5	5	2	1,2	1	IIIc	2	1		1,2
6	4	3	1,2,3	3 gct	IIIc	2,4	1		1,2
7	7	3	1,2	1	IIIc	1,2	2		1
8	6	2	1,2,3	1	IIIc	2	1		1,2
9	5	2	1,2	1	IV	2	1		4
10	6	3	1,3	1	IV	2	1		1
11	2	4	1,3	3 gct	Ia	2	1		4
12	6	3	3	5	IIIc	1,2	1		4,2
13	3	1	1,3	1	I	1,2	1		1
14	5	3	1,3	1	III	1,2	1		1,2
15	8	3	,4	5	IIIc	2	1		1
16	5	3	1,2	1	III	1,2	1		1
17	5	1	1,3	1	I	1,2	1		1,2
18	3	1	1,2,3	3 gct	III	2	1		4

19	4	3	1,2,3,4	4	I	2	1	1,2
20	6	1	1,2,3	1	I	1,2	1	1,2
21	2	4	1,2,3	5	IV	2	1	2,4
22	4	2	1,2,3	1	III	2	1	1
23	6	3	1,2,3	1	IV	1,2	1	4
24	7	3	1,2,4	1	IV	2,4	1	1 -
25	6	1	1,2	1	IIIc	2,4	1	1,2
26	4	3	1,4	3	Ia	2	1	1
27	3	3	1,2,3	2	I	2	1	1,2
28	5	1	1,2,3	3	IV	1,2	1	-
29	6	2	1,3	1	IIIc	2,3	1	1 -
30	5	2	1,2,3	1b	IIIc	2,3	1	1,2
31	6	3	1,2,3	4	III	1,2	1	-
32	2	4	1,2	1b	Ia	2	1	1,2
33	7	1	1,2,3	4	IV	1,2	1	1 -
34	2	4	1,2,3	3	Ivc	2,4	2	1,2
35	8	3	1,2,3,	1c	Ia	2	1	1,2
36	6	1	1,2,3	4	IIIc	2	1	1,2
37	4	2	1,2,3	1	IIIc	2	1	1,2
38	5	1	3,4	4	-	2	1	1,2
39	8	3	1,2,3	1a	Ia	2	1	1,2
40	3	4	4	3	I	2	1	4
41	5	1	4	5	I	2	1	1,2
42	6	2	1,2,3	4	IV	1,2,3	1	1 -
43	7	1	1,2,3	4	IV	1,2	1	1 -
44	6	1	2,3	1	IIIc	1,2	1	-
45	4	3	1,2,3	4	IV	1,2	1	2 -

46	6	3	1,2,3	5	IV	1,2,3	1	1	-
47	7	3	1,2,3	1a	IIIa	2	1		1
48	5	3	1,2,3	1b	IIIb	2	1		1
49	4	3	4	4	Ia	2	1		4
50	4	1	1,2,3	4	IIIc	1,2	1	1	-
51	5	3	1,2,3	1b	IIIc	1,2	1		1,2
52	3	2	1,2,3	1b	IIIc	2	1		1
53	6	3	1,2	1b	Ic	2	1		1
54	3	4	1,2,3	1c	Ic	2	1		4
55	5	3	1		I	1	1		—
56	6	1	1,2,3	1b	IV	1	1		—
57	5	3	1,2,3	5	IIIc	2	1		4
58	6	2	1,2,3	1	IIIc	1,2	1		1,2
59	4	2	1,2,3	4	IIIc	2	1		1
60	5	2	1,2,3	1a	IV	1,2	1	2	—
61	8	3	1,2,3	1a	IIIc	2	1		1,2
62	3	2	1,2,3	1	IIIc	1,2	1		1,2
63	3	2	1,2,3	2	Ia	2	1		4
64	6	3	1,2,3	1	IIIc	2	1		1,2
65	5	1	2,3	4	IV	2	1		1,2
66	5	3	1,2,3	4	III	1,2	1		1,2
67	5	3	1,2,3	1a	IV	2	1		4
68	6	2	1,2,3	1	III	2	1		1
69	6	3	1,2,3	1	IIIc	1,2	1		4
70	2	4	3,4	3	IV	2	1		4
71	3	2	1	3	IIIc	2	1		4
72	4	2	1,2,3	1a	IV	1,2	1		4

73	5	1	1,2,3	1	III	2	1	1,2
74	6	3	1,2,3	1b	IIIc	1,2,4	1	1,2
75	5	2	1,2,3	1a	Ic	2	1	1,2
76	6	1	1,2,3	1b	IIIc	1,2	2	1
77	5	3	1,2,3	1a	IIIc	1,2	1	4
78	5	3	1,4	4	I	2	1	1
79	7	3	1,2,3	1	IIIc	1,2	1	1,2
80	5	2	1,2,3	1b	Ia	2	1	1
81	5	1	1,2,3	1a	IV	1,2	2	4
82	4	2	1	2 bt	Ia	2	1	4
83	5	2	1,2,3	1	IIIc	2	1	4
84	8	2	4	1	Ia	2	1	1
85	4	2	1,2,3	1	IIIc	2	1	1
86	6	2	1,2,3	4	IV	1,2	1	4
87	3	3	1,2,3	3	I	2	1	1,2
88	3	4	1,2,3	1b	Ia	2	1	4
89	4	3	1,2,3	1 bt	IIIc	1,2	1	4
90	6	2	2,3	1	III	2	1	1,2
91	2	4	1,2,3	3	III	1,2,3	1	–
92	5	1	1,2,3	1c	Ic	2	1	1,2
93	5	2	1,2	1b	IIIc	2	1	1,2
94	8	2	1,2,3	1	III	1,2	1	4
95	3	2	1,2,3	3	IIIa	2	1	1,2
96	5	2	1,2,3	4	III	1,2	1	–
97	5	3	1,2,3	1a	IV	1,2	1	1
98	5	3	1,2,3	1a	III	1,2	1	4
99	5	3	1,2,3	1b	IIIc	2	1	1

100	5	1	1,2,3	1b	Ia	2	1	1
101	5	3	1,2,3	1	IIIc	1,2	1	4
102	4	3	1	1b bt	Ia	2	1	1
103	5	1	1,2,3	1a	III	2	1	1,2
104	5	3	2,3	1b	IIIc	1,2	1	1,2
105	3	1	1,2,3	1a	Ia	2	1	4
106	3	2	1,2,3	5	IV	1,2	2	1,2
107	6	2	1,2,3	4	IV	1,2	1	1
108	5	2	1,2,3	1	III	1	1	4
109	6	1	1,2,3	1b	III	2	1	1
110	2	4	1,2,3	4	IV	1,2,3,4	1	4
111	7	3	1,2,3	1	III	1,2	1	4
112	6	1	1,2,3	1	IIIc	2	1	1

S.no	Laprotomy-Results	Adj.Chemo	Toxicity	DFS	DOR- DOF
1	3	2	1,2	2	3
2	2	0	1,2	2	2
3	-	-	1,2	2	2
4	-	-	1	2	1
5	3	1	2	2	3
6	3	1	1	1	1
7	3	1	1	1	2

8	3	1	1,2	2	2
9	4	2	1,2,3	1	3
10	3	1	2,3	3	3
11	2	-	1	3	3
12	3	-	2	1	1
13	3	2	1,3	1	1
14	3	2	1,2	1	2
15	3	-	1,2	2	2
16	3	1	1,2	1	1
17	3	1	1,3	1	1
18	3	2	1,2,3	5	-
19	3	-	1	3	3
20	3	-	1	5	-
21	3	1	1,2	1	1
22	3	1	2	2	3
23	4	1	1	1	3
24	-	-	3	2	3
25	2	1	1	2	3
26	2	-	1,2	2	2
27	3	-	1,2	-	-
28	-	-	1,2	1	-
29	-	-	1,2	3	-
30	3	-	1,2	3	-
31	-	-	1,3	-	-
32	2	1	1,2	3	3
33	-	-	1	-	-
34	3	2	3	2	2

35	3	-	,1	3	3
36	3	2	1	3	3
37	3	1	2	2	2
38	2	-	1	3	3
39	2	1	1,2	3	3
40	2	-	1,2	2	2
41	2	2	1,2	2	2
42	-	-	1,2	1	1
43	-	-	1,2	-	-
44	-	-	1,2	5	-
45	-	-	1,3	5	-
46	-	-	2	1	1
47	3	1	1	2	2
48	3	1	1	1	5
49	2	-	2	5	5
50	-	-	1,2	5	5
51	3	1	1,3	2	2
52	3	-	1	5	5
53	3	1	2	2	2
54	3	1	1,2	2	2
55	-	-	1	2	2
56	-	-	1,2	5	5
57	3	1	3	2	2
58	3	2	1,2	2	2
59	3	1	1	2	2
60	-	-	1,2	5	5
61	3	1	1,3	2	2

62	3	1	1	2	2
63	2	-	1	2	2
64	3	1	,1,2	2	2
65	3	2	1,2	5	5
66	3	1	1,3	2	2
67	4	1	1,	2	2
68	3	2	1	5	5
69	4	2	1	5	5
70	3	1	1,2	2	2
71	3	-	1,2	5	5
72	3	1	1,3	2	2
73	3	1	1,2	-	2
74	3	-	1,2	5	5
75	3	1	1,2	1	1
76	3	1	1	-	1
77	4	1	1	-	1
78	2	1	2	-	1
79	3	1	2	-	1
80	2	-	3	5	5
81	4	1	1,2	-	1
82	2	-	2,3	-	1
83	4	1	1,2	1	1
84	2	-	1,3	-	1
85	3	2	1,2	1	1
86	4	2	1,2	5	5
87	2	-	1	-	-
88	2	-	1	1	1

89	4	2	2	1	1
90	3	2	2	1	-
91	-	-	1,2	-	-
92	3	2	1,2	1	1
93	3	2	1,3	1	1
94	3	-	1,2	5	5
95	3	1	2,3	1	1
96	-	-	1,2	5	5
97	3	2	1,2	-	-
98	4	2	1,3	-	-
99	3	2	1,2	-	-
100	2	-	1	-	-
101	3	2	1	-	-
102	2	-	1,2	-	-
103	3	2	2,3	-	-
104	3	2	1,2	-	-
105	3	-	1,2	-	-
106	3	-	1,2	-	-
107	-	-	1,2	-	-
108	4	1	1,2	-	-
109	3	2	2,3	2	2
110	4	-	1	1	1
111	3	2	1	-	-
112	-	-	1,3	2	2

Age in years	Parity	Clinical - Features		HPE
1 – 9 (1)	Nulliparous (1)	Abd.. mass with distension (1)	I (1)	Epithelial 1A - Serous
10 – 19 (2)	1 -2 Children (2)	Loss of appetite and loss of wt (2)	II (2)	1B Mucinous
20 – 29 (3)	> Children (3)	Pain abdomen (3)	III (3)	1C Endometriod
30 – 39 (4)		Gynaec.complaints (4)	IV (4)	B Border Line (2)
40 – 49 (5)				Germcell Tumor (3)
50 – 59 (6)				Stromalcell Tumor (4)
60 - 69 (7)				Others (5)
70 – 79 (8)				

USG	CXR	Surgery	Laprotomy - Results	DFS
Ascites (1)	NAD (1)	TAH with BSO (1)	Optimal (1)	< 6 months (1)
Solid & Cystic (2)	Other Changes (2)	Omental Bx & Omentectomy	Sup Optimal (2)	6 – 12 months (2)

		(2)		
Liver mets (3)		Peritoneal Bx (3)	Gross residual (3)	> 12 months (3)
Hydronephrosis (4)		Others (4) (Laprotomy & Open & Close)	Open & Close (4)	On going Chemo (4)
Lymph Nodes (5)				Lost Follow- up (5)

Toxicity	
G . I System (1)	
Neuro Toxicity (2)	
Haematological (3)	

MASTER – CHART KEY.